



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61B 17/00, 17/068	A1	(11) International Publication Number: WO 98/17179 (43) International Publication Date: 30 April 1998 (30.04.98)
--------------------------------------------------------------------------------------	-----------	----------------------------------------------------------------------------------------------------------------------------

(21) International Application Number: PCT/GB97/02845

(22) International Filing Date: 15 October 1997 (15.10.97)

(30) Priority Data:
9621622.1 17 October 1996 (17.10.96) GB(71)(72) Applicant and Inventor: GLEESON, Malachy [GB/GB];
Collingwood, South Hill Avenue, Harrow on the Hill,
Middlesex HA1 3PB (GB).

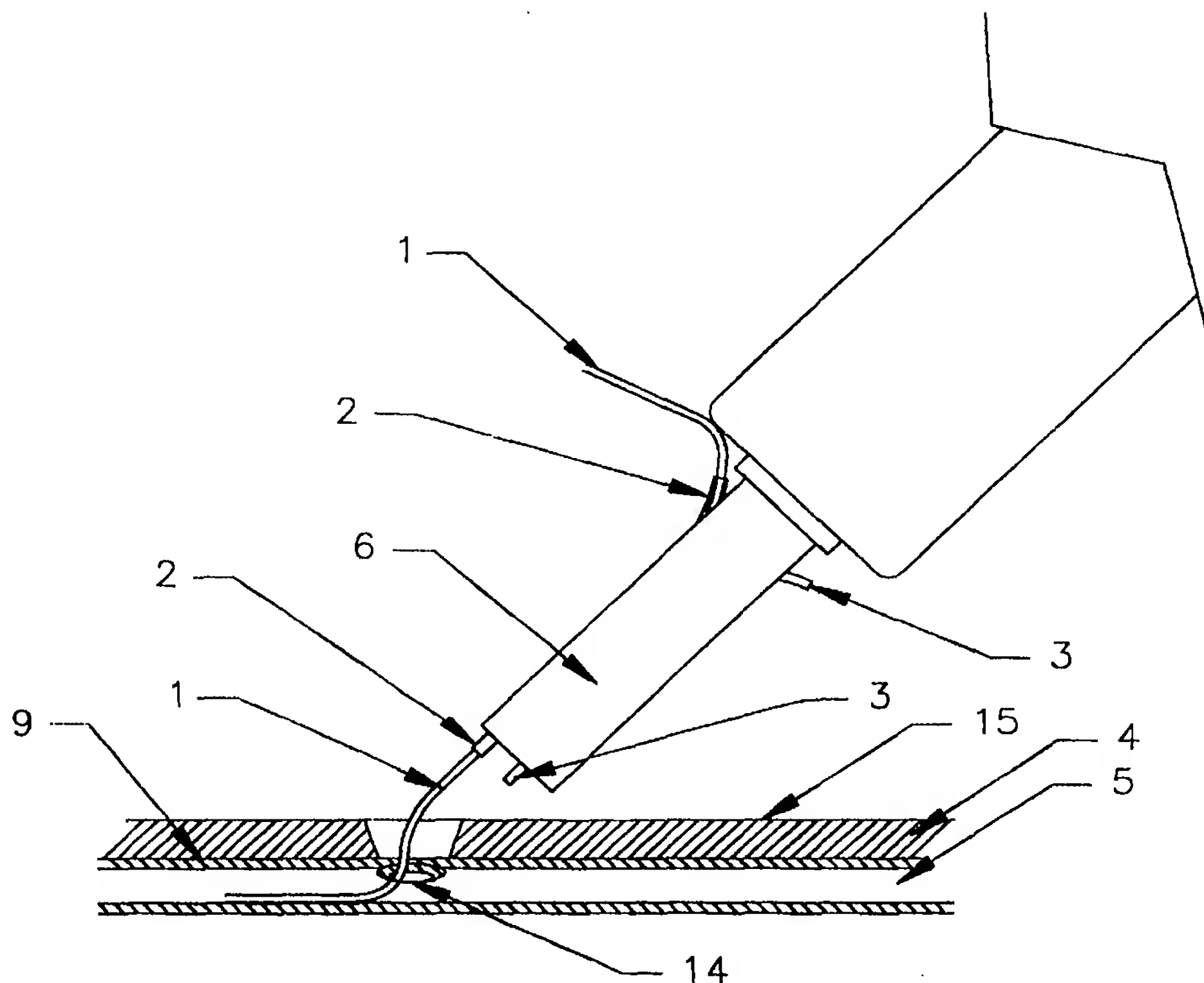
(72) Inventor; and

(75) Inventor/Applicant (for US only): TAYLOR, James [GB/GB];
9 Maple Grove, Droitwich, Worcs. WR9 7QF (GB).(74) Agents: POWELL, Stephen, David et al.; Williams, Powell &
Associates, 4 St. Paul's Churchyard, London EC4M 8AY
(GB).(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE,
GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH,
KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG).**Published***With international search report.*

(54) Title: DEVICE FOR CLOSURE OF A PUNCTURE WOUND

(57) Abstract

A surgical stapling device is described which comprises a shaft (6) with a hollow channel running throughout its length which terminates at its distal end in front of a surgical staple which is housed in the distal end of the stapling device. Closure of a puncture can be achieved after the stapler has been brought into position over a guidewire (1) which has previously been placed into the blood vessel (5) via a percutaneous approach (15, 4). The exact site of the stapling device in relation to the puncture site may be confirmed by advancing a blood vessel puncture site locator tube (2) over the guidewire running through the shaft of the stapler and into the blood vessel puncture site (14). Backflow of blood will be observed. Following either withdrawal of the locator tubing or leaving it in place over the guidewire, the staple is deployed into the walls of the artery (9), and after approximating its opposite walls, is automatically ejected from the stapler. The stapler is then removed from the percutaneous tract over the guidewire which itself is removed when haemostasis is observed.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DEVICE FOR CLOSURE OF A PUNCTURE WOUND

The present invention relates to a device for locating and sealing a puncture wound in animal and human tissue and the related method. A particular example is a vascular puncture.

An ever increasing number of vascular interventional procedures are being undertaken by cardiologists and radiologists. With the growing use of both diagnostic and therapeutic procedures requiring percutaneous vascular access, a real demand exists for a method and device for accurately locating and closing the puncture site in the blood vessel, post interventional procedure.

Due to ease of access, the most common site selected for these percutaneous arterial interventional procedures is the femoral artery. The normal procedure is to insert an angiographic needle into the femoral artery. This is followed by the insertion of a guide wire and over this guide wire successive dilators are passed percutaneously into the artery in order to widen the puncture in the artery sufficiently to allow the sheath of optimal diameter for the diagnostic or therapeutic procedure to be inserted. Through this sheath is then inserted the required catheter or interventional device in order to perform the required diagnostic or therapeutic procedure on the patient.

At the end of the procedure above, the standard treatment on removal of the sheath involves digital pressure on the artery, supplemented with external compression such as sandbags, pneumatic extension cuffs, or adjustable vice-like devices which may be graduated to apply different degrees of pressure on the skin over the puncture site. This method results in the occlusion of the puncture site by thrombosis of blood in the wall of the puncture site and haemostasis in the percutaneous tract. It causes considerable discomfort for the patient and is associated with a long period of immobilisation. Unpredictable post-procedural haemorrhaging during time periods varying from hours to days after the intervention are not uncommon, and may even be fatal for the patient. The additional healthcare cost in dealing with this complication may be considerable.

A series of devices have been invented to address some of these problems by Datascope Corp. U.S.A., PerClose Corp. U.S.A., Kensey Nash Corp. U.S.A. and Bard Corp. U.S.A.

The present invention which is, however, independent of the exact procedure and of which type of wound is involved, discloses a new method and a new device for sealing a tissue wall puncture by approximating the walls of the tissue in such a way as to obliterate the puncture site. The present invention will find use for vascular puncture wounds, as well as in other medical procedures which rely on percutaneous access to hollow organs such as laparo-scopic procedures, arthroscopic procedures, and the like. It will also find use in closing body orifices approached directly by the device or approached through body cavities or organs.

The new method involves the use of a surgical stapler which includes means to permit use at visually inaccessible sites.

Accordingly, the invention proposes a surgical stapler having a stapler head at its distal end, comprising guide means which can be used to constrain the stapler to move along a pre-positioned guide wire to reach a location along the path of said guide wire. The invention is of particular use at visually inaccessible surgical sites.

The invention also proposes a surgical stapler, for use at visually inaccessible vascular sites, having a stapler head at its distal end, and comprising guide means which can be used to constrain the stapler to move along a pre-positioned guide wire to reach a location along the path of said guide wire, and locator means which project forwardly of the stapler head which enable blood flow to be sensed within a blood vessel with consequential location of the stapler head adjacent the exterior of said blood vessel.

After the intervention the guide wire may have an incremental marking measurement scale along its length, allowing the operator to estimate precisely the amount of guide wire which is placed within the blood vessel. After the interventional procedure serial dilators may be placed over the guide wire and used to dilate the subcutaneous tract down to the level of the external wall of the arterial puncture to allow access by the stapler. The dilator may

contain a radio-opaque marker and also a measurement scale which allows the accurate measurement of the length of the percutaneous tract from the skin level to the outer surface of the blood vessel puncture site.

As an alternative method of locating the puncture accurately, the dilator may have a fine bore plastic tube running through its length which passes over the guidewire. The calibre of this plastic tubing is such that it will be sufficiently small to pass into the blood vessel. This tubing may be fixed to the dilator and protrudes for approximately 1-6 mm and preferably 2-4 mm beyond the distal end of the tissue tract dilator. When blood is observed pulsing back from the distal end of this tubing on to the skin, it can be taken to signify that the tube has entered the blood vessel and consequently the dilator has reached the outer surface of the blood vessel. When this occurs, the exact depth of the percutaneous tract may be measured. Transmission of a pulsation via the dilator to operator may be taken as further evidence that the dilator is resting against the outer wall of the artery. After completion of dilation of the tract, the dilator is removed over the guidewire which itself is left in place so that the inventive stapler can then be used.

Alternatively, the fine bore tube may be fixed within the stapler itself with the same degree of projection. In either case, the distal end of the tube may have a longitudinal slit into which the guidewire may enter as it curves into the artery.

In order that the invention shall be clearly understood, exemplary preferred embodiments are now described with reference to the drawings, in which:

Figure 1 is a schematic view of an apparatus according to the present invention being moved into position;

Figure 2 is a schematic view of the surgical stapling device which has been brought into position for use over the guide wire and its position may be indirectly confirmed by observing the back flow of blood through the blood vessel puncture site locator tubing;

Figure 3 is a cross-sectional view of an artery with the guide wire and stapler still in place; and

Figure 4 is a schematic view in section of the distal end of an apparatus constructed according to the present invention.

A new vascular stapling device is advanced over a guidewire 1 (see Fig. 1) previously inserted. The shaft of the stapling device which may be rigid or flexible slides down along the guidewire through the dilated subcutaneous tissue 4 tract and rests on the wall of the blood vessel 9. The shaft 6 of the stapling device may be calibrated in order to confirm to the operator that the previously measured length of the tract has been travelled by the shaft. Running through the shaft of the stapling device may be one or two blood vessel puncture site locating flexible plastic tubes 2, which may be advanced over the guidewire 1. These tubes may be located in the front and/or behind and/or beside the one or more staples to be delivered to close the puncture site. This plastic tubing may be calibrated and its exact relationship with the tip of the stapling device is known because of calibrated graduated measured markings or other method of marking along its length. In addition this tubing may be radio-opaque further facilitating identifying its position in relation to the puncture site.

As the distal end of the stapling device (Fig.2) comes to lie on the blood vessel 9, an approximate 4mm protrusion of the blood vessel puncture site locator plastic tubing 2, 3 may enter through the puncture site 14 into the lumen of the blood vessel 5. Pulsating blood will then traverse back through the tubing, through the shaft 6 of the stapling device, and out through the proximal lumen of the tubing 2, 3. This can be taken as an indication that the tip of the stapling device rests against the outer blood vessel wall 9 at the puncture site 14. Transmission of a pulsating feeling from artery via stapler to operator may be taken as further evidence that the stapler is resting against the outer wall of the artery. A second plastic tubing 3 which may be located behind the first or second staple may also be advanced into the arterial puncture to confirm exact localization and alignment of the stapler, if so desired.

Following confirmation of the stapler position, the blood vessel locator tubing 2, may be pulled back along the guide wire 1 into the shaft of the stapler. The pulsation of blood then ceases. At this point the distal end of the stapler which is orientated by the guidewire 1 is now placed firmly against the blood vessel wall 9. As the shaft 6 of the stapling device is brought towards perpendicular position (see Fig. 2) in relation to the skin 15, it will result in the guidewire assuming an angle approaching or greater than 90 degrees and this may cause the puncture hole to be stretched and to change from a round shape to become more oblong. This has the effect of bringing the opposite walls closer together. A safety latch on the handle of the stapler is released and graduated pressure is then applied to the handle of the stapler, which results in the two needle sharp legs (see Fig. 3) of one or more separate staples placed in parallel to be deployed simultaneously (or consecutively, if delivery mechanism is so designed) in order to engage the blood vessel wall. In the case where two staples are delivered, the four staple points (two points per staple) are ejected either in the longitudinal or transverse axis (if stapler is rotated 90 degrees) of the blood vessel and their accurate positioning is assisted by the previous measurements described above and by the fact that the staple delivery system is held on a guide wire. The one or more pre-formed staples may be totally deployed into the wall of the blood vessel 9 while at the same time undergoing a predetermined deformation 7 as defined by the shape of the staple former 8 mechanism in the stapler head.

If required, an angiogram may be performed via a side arm on the plastic tubing which traverses the length of the stapling shaft. Contrast medium may be injected into the blood vessel, provided the tubing is advanced along the guide wire and into the blood vessel. Alternatively, the contrast medium may be injected at the outer surface of the blood vessel if so desired in order to reconfirm the exact positioning of staples. Also a radio opaque marker may be present in the tip and shaft of the stapling device and this combined with the radio opaque nature of the staples themselves may facilitate further confirmation that the desired placement has taken place.

The trigger mechanism which advances the single or double staple pushers (which are part of the staple former mechanism 8) (see Fig. 4) may be further advanced and this results in one or both staples being further deformed to the desired shape and ejected by the formed

shape unload spring 12 from the distal end of the stapler simultaneously (or consecutively if stapler so designed), with the transverse member of each staple perpendicular to the long axis of the blood vessel. Alternatively, they may be discharged in parallel to the long axis of the blood vessel resulting in a transverse closure of the puncture site. Closure of the staples will result in the approximation of the opposite walls of the puncture site. The end result will be a minimum of one staple (preferably two) closing the puncture site by means of deformation of two metal or absorbable staples (or staples made from other non-absorbable implantable material) in such a way as to approximate the walls of the puncture site.

During the final closing action of the staples, the operator may decide whether or not to close the puncture site around the guide wire. Normally, the guide wire will be of sufficiently fine calibre so as to result in minimal subsequent problems of bleeding on its removal. The operator may find it desirable to leave the guide wire in place after deployment of the staple or staples if he believes that there is a danger that the vascular procedure which has been carried out will require a re-intervention within a defined time period. If however, the operator is confident that no subsequent intervention in the immediate post-procedure period will be warranted, the guide wire may be removed prior to the final formation of the staple resulting in the closure of the puncture site. Alternatively, the total procedure of deployment, deformation and ejection of the staple or staples from the stapling device may be carried out in one continuous movement over the guidewire which may be removed immediately after deployment.

Two spring-like or other mechanisms 12 will eject the staples either towards the midline of the stapler shaft or towards the lateral walls of the stapler when the final trigger activation squeeze mechanism has been completed. This will result in releasing the staples from the distal end of the stapler and allow withdrawal of the stapler shaft from the percutaneous tract over the guide wire with ease.

The apparatus comprises a frame and shaft 6 (which may be flexible) which stores at least one surgical staple at its distal portion. The shaft has at least one purposely built hollow channel 10, 13 (see Fig. 4) running throughout its length which allows the shaft 6 to be advanced over a guide 1 which has previously been placed percutaneously into a blood

vessel lumen 5 in order to secure vascular access as previously described for percutaneous intravascular interventions. This purposely built channel (or channels) 10, 13 may also be used to advance blood vessel puncture site locator tubing 2, 3 along guidewire or by itself into blood vessel puncture site 14. The frame and shaft (which has been advanced over the guidewire) house a staple pushing apparatus (of which the staple forming mechanism 8 may be a part) which advances the staple or staples into the margins of the puncture site on the outer surface of the blood vessel (see Fig. 3). At the distal end of the shaft may be an anvil means 11 for closing the staple in a manner that causes the staple to penetrate the wall 9 of the blood vessel. Subsequent deformation of the staple about the anvil 11 will result in the bringing together of the opposite walls of the puncture site. The staple advancing system (of which the staple former 8 may be a part) may extend from the frame through the shaft 6 of the device and may be activated by a trigger mechanism attached to the frame and forming a part thereof.

The surgical staples may be stored in parallel beside each other, with the transverse member of the staple perpendicular to the longitudinal axis of the shaft. The shaft may be rotatable. This point of rotation may begin at the junction between the frame and the shaft. The distal end of the shaft may have a pivoting joint. Throughout the length of the shaft, at least one elongated rod may be positioned within the shaft to act as a pusher to deploy one or preferably two staples simultaneously or consecutively and in parallel while the stapler is positioned over the guide. The means of advancing the staples distally may be controlled by the operator at a proximal location. The distal end of the staple former 8 engages the staple or staples and advances the staple or staples in the distal direction. The staple former which forms the distal end of the staple pusher has at its distal end a plate member, and the plate member may be dimensioned, configured and arranged to engage and advance the staple distally. The staple storage area at the distal end of the shaft includes at least one but preferably two anvils 11 (see Fig. 3) which each engage a staple and deform it to a predetermined configuration.

A surgical staple is adapted to bring together the opposite walls of a puncture site in a blood vessel. The staple may comprise of a length of wire and two perpendicular legs which are joined by a transverse member. These perpendicular legs are sharpened and will

penetrate the outer wall of the blood vessel. Deformation of the bridge portion of the staple will result in both legs of the staple deforming in arcuate manner and facing in a direction generally towards the centre of the transverse wire portion. Deformation of the staples occurs over each anvil and results in the shortening of the transverse member which ultimately results in the opposite walls of the puncture site being advanced towards each other. The leg members of the staple are folded in such a manner so as not to interfere with each other. The surgical staple may be made from stainless steel, titanium or any absorbable or non-absorbable implantable polymer, i.e. any suitable metal or non-metal.

On completing the closure mechanism of the stapler handle, the indicator on the handle (if present) may show that the staple closure cycle is complete and on release of the handle, the deforming push rods may retract into the shaft of the stapler. This retraction movement of the push rods may cause a spring 12 or other mechanism on the side of the stapler shaft wall (which was deformed by the advancing staple former) to return to its original shape. This spring-back effect may result in one or both of the fully formed staples being ejected from their housing in the distal end of the stapler. Since the staples are now free of the stapling device nose, the staple device itself may now be easily removed from the percutaneous tract along the guide wire.

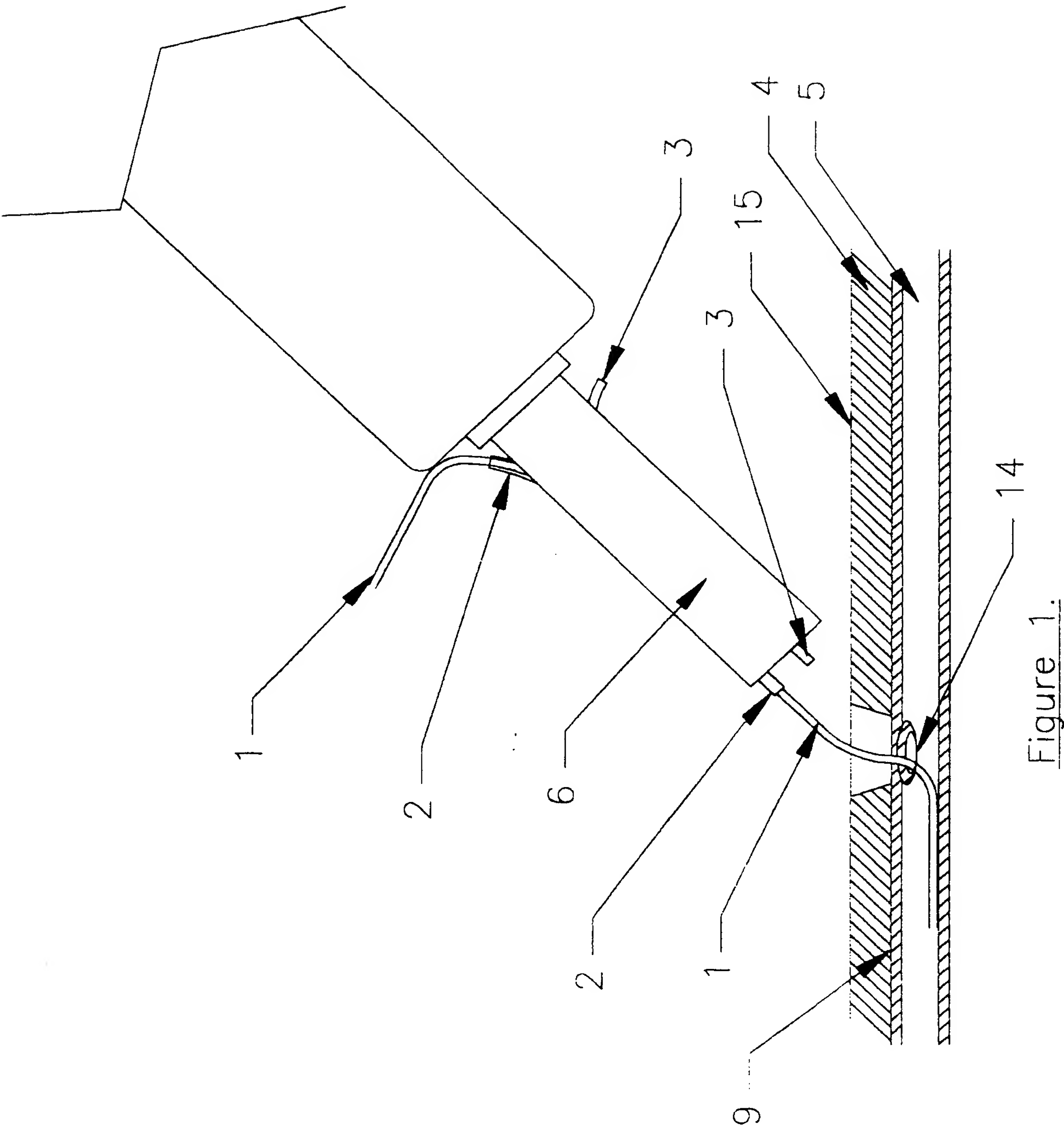
The procedure described above may be carried out using a kit comprising of a surgical staple, guide wire, fine bore plastic tubing for performing an angiogram and localizing the position of blood vessel puncture site in relation to the stapler, a dilator with a hollow channel and graduated markings on its outer surface which can be detected radiologically, a connector side arm for the fine bore tubing through which saline or contrast medium may be injected. Components may be supplied as part of a kit or they may be supplied in a blister type or other packaging.

CLAIMS

1. A surgical stapler having a stapler head at its distal end, comprising guide means which can be used to constrain the stapler to move along a pre-positioned guide wire to reach a location along the path of said guide wire.
2. A surgical stapler, for use at visually inaccessible vascular sites, having a stapler head at its distal end, and comprising guide means which can be used to constrain the stapler to move along a pre-positioned guide wire to reach a location along the path of said guide wire, and locator means which project forwardly of the stapler head which enable blood flow to be sensed within a blood vessel with consequential location of the stapler head adjacent the exterior of said blood vessel.
3. A surgical stapler as claimed in claim 1 or 2, wherein said guide means comprise a channel extending through the stapler, one end of each channel being at said distal end.
4. A surgical stapler as claimed in claim 3 wherein said channel is of sufficient cross-section to accommodate both a guide wire and a locator means.
5. A surgical stapler as claimed in claim 2,3 or 4, wherein the locator means is a fine-bore rigid or flexible tube, small enough to enter a vascular organ.
6. A surgical stapler as claimed in any of claims 2 to 5, wherein the locator means projects beyond the stapler head by a distance of 1 to 6mm.
7. A surgical stapler as claimed in any preceding claim, wherein the stapler ejects one or two staples at each actuation.
8. A method of sealing a puncture-wound in animal tissue comprising inserting a guide wire through the puncture wound, and guiding a surgical stapler along the wire until the stapler head at its distal end reaches said puncture site, operating said stapler to staple together the opposing edges of the puncture site, and withdrawing said stapler.

9. A method as claimed in claim 8, wherein said wound is a vascular puncture and the position of the external surface of the vascular organ to be stapled is determined by sensing the blood pulsation and/or blood flow.

10. A method as claimed in claim 9, including the step of moving a fine-bore rigid or flexible tube along said guide wire until its distal end enters the vascular organ and blood pulses back through the proximal end.



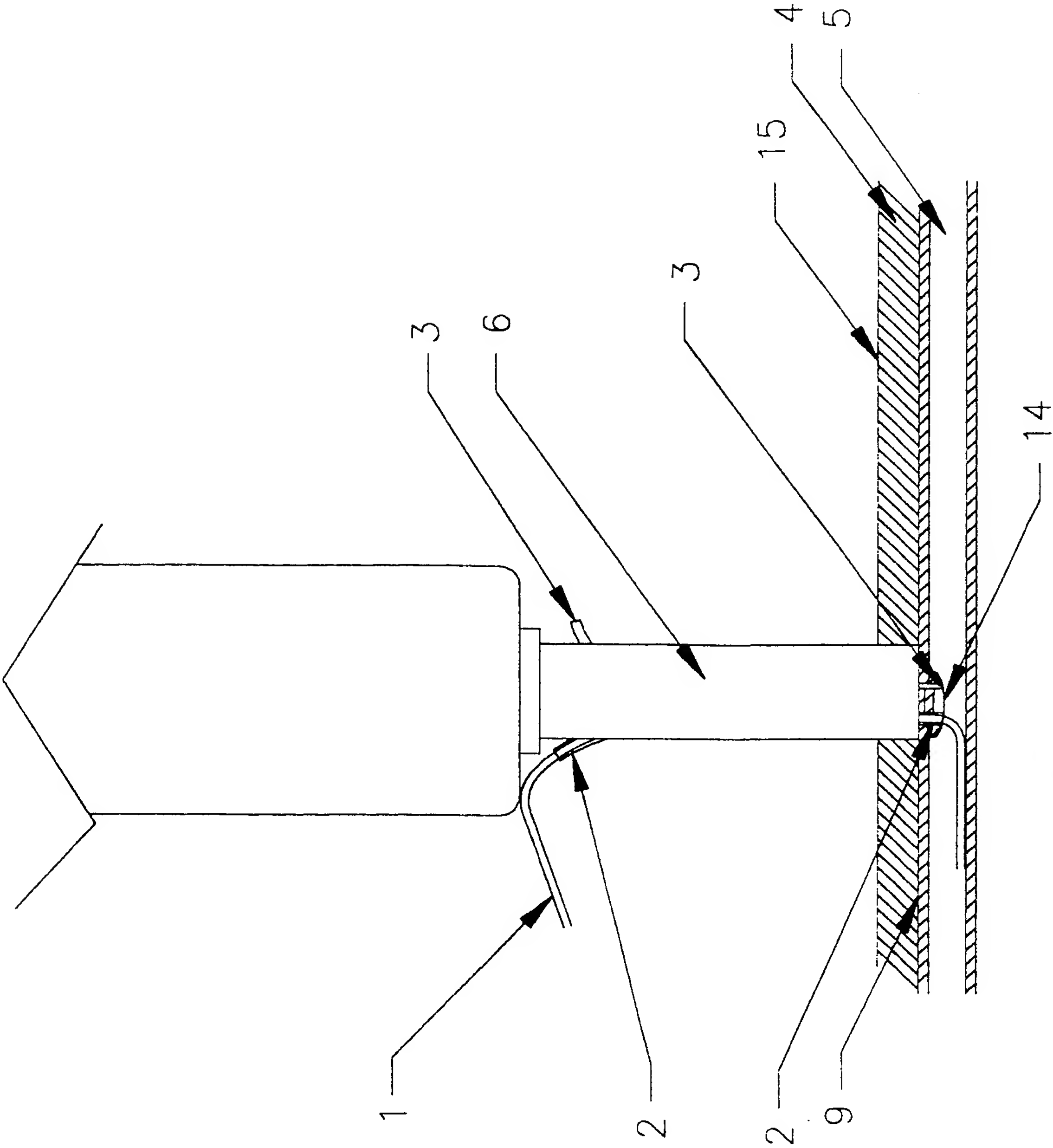


Figure 2.

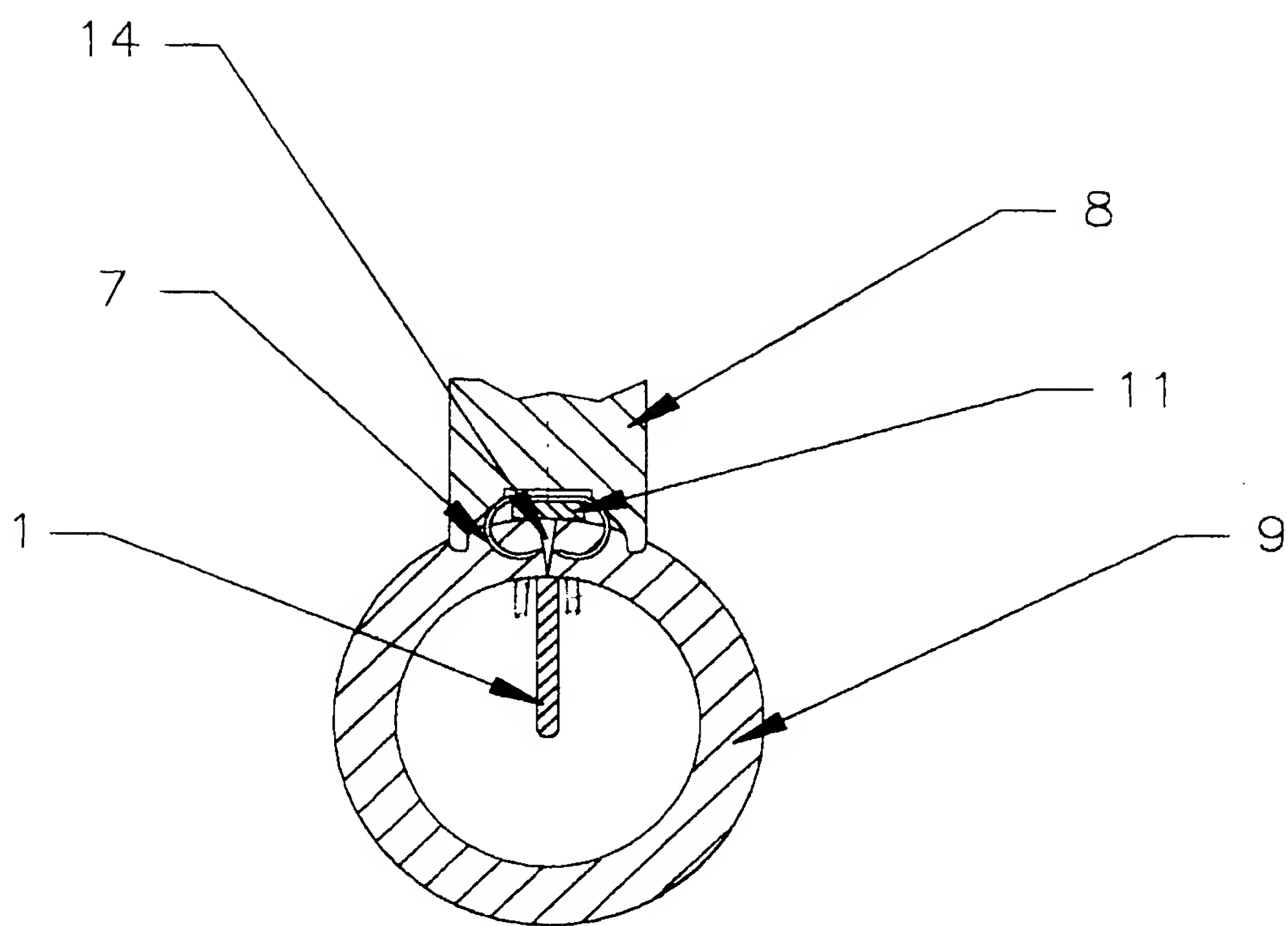


Figure 3.

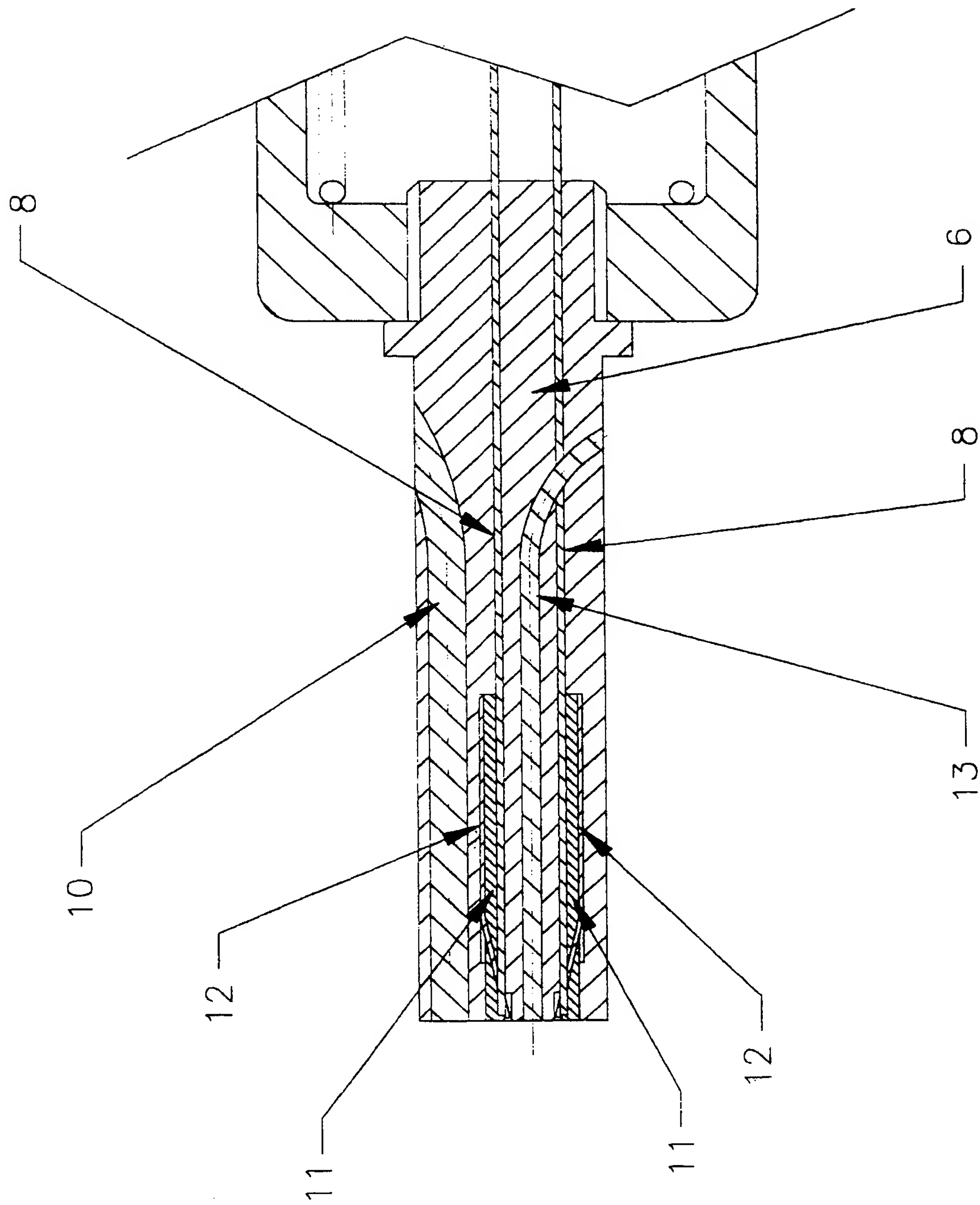


Figure 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02845

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61B17/00 A61B17/068

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 292 332 A (LEE) 8 March 1994 see column 5, line 33 - line 36; figure 4 ---	1-7
A	US 5 536 251 A (EVARD) 16 July 1996 see column 8, last paragraph - column 10, paragraph 1; figures 5,6 ---	1,2
A	US 5 527 322 A (KLEIN) 18 June 1996 see figure 8 ---	1-7
A	US 4 771 782 A (MILLAR) 20 September 1988 ---	
P,X	WO 97 20505 A (LOMA LINDA) 12 June 1997 see page 10, line 9; figures 14,18 ---	1,2,5-7
P,X	EP 0 756 851 A (USSC) 5 February 1997 see page 9 ---	1-7
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 January 1998

Date of mailing of the international search report

23.01.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Barton, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/02845

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 774 237 A (USSC) 21 May 1997 see figures 15,21 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/02845

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-10
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5292332 A	08-03-94	US 5443481 A	22-08-95
US 5536251 A	16-07-96	US 5425705 A	20-06-95
		US 5452733 A	26-09-95
		US 5618307 A	08-04-97
		US 5626607 A	06-05-97
		AU 1433295 A	17-07-95
		CA 2179897 A	06-07-95
		EP 0737083 A	16-10-96
		WO 9517919 A	06-07-95
		AU 6024594 A	14-09-94
		EP 0684781 A	06-12-95
		JP 8511694 T	10-12-96
		WO 9418881 A	01-09-94
		US 5571215 A	05-11-96
		US 5569274 A	29-10-96
		US 5613937 A	25-03-97
		US 5682906 A	04-11-97
US 5527322 A	18-06-96	AU 8083994 A	29-05-95
		EP 0727965 A	28-08-96
		JP 9504966 T	20-05-97
		WO 9513021 A	18-05-95
US 4771782 A	20-09-88	AU 8335787 A	01-06-88
		DE 3784074 A	18-03-93
		EP 0332649 A	20-09-89
		JP 2602938 B	23-04-97
		JP 3505822 T	19-12-91
		WO 8803422 A	19-05-88
		US 4850358 A	25-07-89
		US 4966148 A	30-10-90
		US 5046497 A	10-09-91
WO 9720505 A	12-06-97	NONE	
EP 756851 A	05-02-97	CA 2182070 A	04-02-97
EP 774237 A	21-05-97	US 5674231 A	07-10-97
		CA 2188210 A	21-04-97